Supplementary data

Table S1. CANTAB descriptive statistics.

	Group	Mean	SD	T-test t	df	p
PAL-TE (Total Error adjusted)	HC (n=10)	10.2	3	-2.115	28	**0.043**
	GO (n=20)	19.4	13.4			
PAL-TE6 (TE six shapes adjusted)	HC	3.2	1.8	-1.806	28	0.082
	GO	7.5	7.3			
PAL – FT (First trial memory score)	HC	17.0	1.6	0.084	28	0.0933
	GO	16.9	3.5			
PAL – MT (mean of Tentative)	HC	1.3	0.1	-3.108	28	**0.004**
	GO	1.9	0.6			
SWM - BE (Between errors Total)	HC	14.8	5.7	-2.206	28	**0.036**
	GO	26.0	15.4			
SWM - S (Strategy)	HC	33.6	4.8	0.411	28	0.684
	GO	32.8	5.1			
RVP -A	HC	0.9	0.03	3.029	28	**0.005**
	GO	0.8	0.03			
RVP - ML (Mean latency)	HC	500.0	94.5	1.230	28	0.229
	GO	459.4	82.1			

Table S2. TCI descriptive statistics.

Temperaments	Group	Mean	SD	t	T-test df	p	Characters	Group	Mean	SD	t	T-test df	p
TCI-NS1	HC	5.800	2.616	-1.05	28	0.323	TCI-SD1	HC	7.400	0.516	1.33	28	0.192
	GO	6.800	2.546					GO	6.800	1.361			
TCI-NS2	HC	2.810	1.529	-2.74	28	**0.011**	TCI-SD2	HC	5.200	1.229	0.92	28	0.362
	GO	5.500	2.911					GO	4.600	1.847			
TCI-NS3	HC	5.000	1.333	1.39	28	0.174	TCI-SD3	HC	3.600	1.430	-1.74	28	0.092
	GO	4.000	2.052					GO	4.400	1.046			
TCI-NS4	HC	4.000	0.667	-0.95	28	0.346	TCI-SD4	HC	6.200	1.033	0.58	28	0.561
	GO	4.810	2.609					GO	5.600	3.119			
TCI-NS TOT	HC	17.60	3.373	-1.40	28	0.170	TCI-SD5	HC	10.40	1.838	1.39	28	0.173
	GO	21.10	7.433					GO	9.200	2.375			
TCI-HA1	HC	3.800	2.044	-0.62	28	0.534	TCI-SD-TOT	HC	32.80	2.150	1.01	28	0.319
	GO	4.300	2.055					GO	30.50	6.947			
TCI-HA2	HC	4.400	1.430	0.41	28	0.679	TCI-C1	HC	7.000	1.155	1.43	28	0.163
	GO	4.100	2.024					GO	5.900	2.269			
TCI-HA3	HC	3.800	2.044	1.55	28	0.131	TCI-C2	HC	6.800	0.422	5.14	28	<.001
	GO	2.605	1.951					GO	4.100	1.619			
TCI-HA4	HC	2.400	0.843	0.21	28	0.831	TCI-C3	HC	7.400	0.843	3.24	28	**0.003**
	GO	2.225	2.482					GO	6.200	1.005			
TCI-HA TOT	HC	14.40	5.797	0.53	28	0.597	TCI-C4	HC	9.400	1.265	1.69	28	0.101
	GO	13.20	5.800					GO	8.200	2.042			
TCI-RD1	HC	7.800	1.229	1.90	28	0.068	TCI-C5	HC	8.200	0.422	3.24	28	**0.003**
	GO	6.600	1.789					GO	7.000	1.124			
TCI-RD2	HC	7.000	0.943	4.60	28	<.001	TCI-C TOT	HC	38.80	2.044	3.69	28	<.001
	GO	4.300	1.720					GO	31.300	6.208			
TCI-RD3	HC	4.400	1.075	3.56	28	**0.001**	TCI-ST1	HC	4.400	2.459	-1.29	28	0.207
	GO	2.800	1.196					GO	5.900	3.227			
TCI-RD TOT	HC	19.20	2.348	4.06	28	<.001	TCI-ST2	HC	3.200	1.229	-2.20	28	**0.036**
	GO	13.70	3.922					GO	4.900	2.269			
TCI-P	HC	2.600	1.713	-3.24	28	**0.003**	TCI-ST3	HC	2.400	1.430	-0.39	28	0.694
	GO	5.000	2.000					GO	2.700	2.155			
							TCI-ST-TOT	HC	10.00	2.749	-1.59	28	0.122
								GO	13.50	6.605			

Table S3. Correlation between HAM-A and TCI dimensions in GO patients

TCINS1	Pearson's r p-value	0.386 0.093	TCIRD1	Pearson's r p-value	0.617** 0.004	TCIC1	Pearson's r p-value	−0.221 0.350
TCINS2	Pearson's r p-value	0.524* 0.018	TCIRD2	Pearson's r p-value	0.666** 0.001	TCIC2	Pearson's r p-value	0.085 0.723
TCINS3	Pearson's r p-value	0.463* 0.040	TCIRD3	Pearson's r p-value	0.355 0.125	TCIC3	Pearson's r p-value	0.241 0.305
TCINS4	Pearson's r p-value	0.546* 0.013	TCIRDTOT	Pearson's r p-value	0.682*** <.001	TCIC4	Pearson's r p-value	0.263 0.262
TCINSTOT	Pearson's r p-value	0.658** 0.002	TCIP	Pearson's r p-value	−0.240 0.308	TCIC5	Pearson's r p-value	0.433 0.057
TCIHA1	Pearson's r p-value	−0.072 0.764	TCISD1	Pearson's r p-value	0.171 0.471	TCICTOT	Pearson's r p-value	0.159 0.504
TCIHA2	Pearson's r p-value	0.048 0.842	TCISD2	Pearson's r p-value	0.320 0.169	TCIT1	Pearson's r p-value	0.192 0.418
TCIHA3	Pearson's r p-value	−0.618** 0.004	TCISD3	Pearson's r p-value	0.434 0.056	TCIT2	Pearson's r p-value	−0.047 0.844
TCIHA4	Pearson's r p-value	−0.138 0.563	TCISD4	Pearson's r p-value	−0.546* 0.013	TCIT3	Pearson's r p-value	0.040 0.868
TCIHATOT	Pearson's r p-value	−0.274 0.243	TCISD5	Pearson's r p-value	−0.463* 0.040	TCITTOT	Pearson's r p-value	0.090 0.704
			TCISDTOT	Pearson's r p-value	−0.215 0.363			

* p < .05, ** p < .01, *** p < .001

Table S4. Correlation between NTs expression and CANTAB scores in GO patients.

		m/proBDNF		m/proNGF	
		Serum	**Tears**	**Serum**	**Tears**
PAL - TE	*Pearsons's r* p-value	**0.665**</br>**0.009**	**0.712**</br>**0.002**	**-0.536***</br>**0.015**	**-0.692**</br>**0.003**
	Spearman's rho p-value	**0.371**</br>**0.235**	0.559*</br>0.038	**-0.609**</br>**0.002**	**-0594**</br>**0.025**
PAL - TE6	*Pearsons's r* p-value	**0.849***</br>**< .001**	**0.683**</br>**0.004**	-0.346</br>0.136	-0.681**</br>0.004
	Spearman's rho p-value	**0.714**</br>**0.009**	**0.751***</br>**0.033**	-0.400</br>0.100	-0.892***</br>< .001
PAL - FT	*Pearsons's r* p-value	-0.198</br>0.498	-0.654**</br>0.006	**0.725***</br>**< .001**	**0.865***</br>**< .001**
	Spearman's rho p-value	-0.429</br>0.165	-0.679**</br>0.008	**-0.713**</br>**0.004**	**-0.655**</br>**0.003**
PAL - MT	*Pearsons's r* p-value	0.457</br>0.100	0.632**</br>0.009	**-0.617**</br>**0.004**	**-0.642**</br>**0.007**
	Spearman's rho p-value	0.371</br>0.235	0.536*</br>0.048	**0.750***</br>**< .001**	**-0.642***</br>**0.013**
SWM - BE	*Pearsons's r* p-value	0.337</br>0.239	0.358</br>0.173	0.103</br>0.666	0.115</br>0.672
	Spearman's rho p-value	0.314</br>0.320	0.536*</br>0.048	-0.200</br>0.426	0.071</br>0.808
SWM - S	*Pearsons's r* p-value	0.112</br>0.703	0.437</br>0.090	0.083</br>0.728	-0.335</br>0.204
	Spearman's rho p-value	0.145</br>0.653	0.306</br>0.287	-0.181</br>0.463	-0.504</br>0.066
RVP - A	*Pearsons's r* p-value	-0.881***</br>< .001	-0.162</br>0.549	-0.173</br>0.465	0.217</br>0.420
	Spearman's rho p-value	-0.928***</br>< .001	-0.360</br>0.206	-0.134</br>0.595	0.252</br>0.385
RVP - ML	*Pearsons's r* p-value	**-0.631***</br>**0.015**	**-0.580***</br>**0.018**	-0.223</br>0.344	-0.259</br>0.332
	Spearman's rho p-value	**-0.714**</br>**0.009**	**-0.750**</br>**0.002**	-0.133</br>0.598	-0.071</br>0.898

* p < .05, ** p < .01, *** p < .001.

Table S5. Correlation between NTs expression and TCI scores in GO patients.

		m/proBDNF		m/proNGF	
		Serum	**Tears**	**Serum**	**Tears**
TCI – NS1	*Pearsons's r*	**-0.879*** **	**-0.779** **	-0.132	0.225
	p-value	**< 0.001**	**0.001**	0.578	0.401
	Spearman's rho	**-0.812** **	**-0.703** **	0.034	0.180
	p-value	**0.001**	**0.005**	0.894	0.538
TCI – NS2	*Pearsons's r*	-0.206	0.461	**-0.706*** **	**-0.688** **
	p-value	0.521	0.097	**< 0.001**	**0.003**
	Spearman's rho	-0.265	0.273	**-0.653** **	**-0.545***
	p-value	0.406	0.345	**< 0.003**	**0.044**
TCI – NS3	*Pearsons's r*	-0.648*	-0.302	-0.171	-0.303
	p-value	0.023	0.295	0.470	0.255
	Spearman's rho	-0.551	-0.327	-0.017	-0.109
	p-value	0.063	0.253	0.947	0.711
TCI – NS4	*Pearsons's r*	-0.085	-0.159	-0.331	-0.170
	p-value	0.792	0.588	0.180	0.562
	Spearman's rho	-0.116	-0.218	-0.136	-0.309
	p-value	0.720	0.454	0.590	0.283
TCI – NS TOT	*Pearsons's r*	-0.802***	-0.030	-0.461	-0.384
	p-value	< 0.001	0.912	0.054	0.141
	Spearman's rho	-0.771**	-0.199	-0.326	-0.384
	p-value	< 0.003	0.495	0.186	0.141
TCI – HA1	*Pearsons's r*	-0.263	0.214	0.012	-0.462
	p-value	0.363	0.432	0.961	0.071
	Spearman's rho	0.029	0.200	-0.068	-0.381
	p-value	0.929	0.493	0.788	0.178
TCI – HA2	*Pearsons's r*	-0.112	0.043	0.758***	0.154
	p-value	0.702	0.875	< 0.001	0.568
	Spearman's rho	-0.058	0.180	0.726***	-0.090
	p-value	0.858	0.538	< 0.001	0.760
TCI – HA3	*Pearsons's r*	0.801***	0.370	0.342	-0.464
	p-value	<0.001	0.158	0.140	0.070
	Spearman's rho	0.754**	0.306	0.417	-0.684**
	p-value	0.005	0.287	0.085	0.007
TCI – HA4	*Pearsons's r*	-0.315	-0.204	0.099	-0.433
	p-value	0.272	0.448	0.678	0.094
	Spearman's rho	-0.330	-0.075	0.026	-0.467
	p-value	0.077	0.799	0.920	0.092
TCI – HA TOT	*Pearsons's r*	0.035	0.152	0.427	-0.467
	p-value	0.904	0.573	0.060	0.119
	Spearman's rho	0.143	0.429	0.267	-0.678**
	p-value	0.658	0.126	0.285	0.008
TCI – RD1	*Pearsons's r*	-0.636*	0.058	-0.396	-0.491
	p-value	0.026	0.830	0.084	0.053
	Spearman's rho	-0.647*	0.218	-0.376	-0.272
	p-value	0.023	0.454	0.124	0.346
TCI – RD2	*Pearsons's r*	**-0.947*** **	**-0.514***	0.146	0.468
	p-value	**< 0.001**	**0.031**	0.563	0.067
	Spearman's rho	**-0.971*** **	**-0.505**	0.170	0.598*
	p-value	**< 0.001**	**0.065**	0.499	0.024
TCI – RD3	*Pearsons's r*	-0.560	-0.180	0.273	-0.006
	p-value	0.058	0.537	0.244	0.983
	Spearman's rho	-0.500	-0.055	0.301	0.018
	p-value	0.098	0.852	0.266	0.950
TCI – RD TOT	*Pearsons's r*	-0.907***	-0.220	0.036	0.020

	p-value	< 0.001	0.412	0.887	0.955
	Spearman's rho	-0.943***	-0.357	0.151	0.178
	p-value	<0 .001	0.210	0.551	0.452
TCI – P	*Pearsons's r*	-0.042	-0.769***	0.303	0.686**
	p-value	0.888	<0 .001	0.195	0.003
	Spearman's rho	-0.042	-0.661**	0.410	0.568*
	p-value	0.888	0.010	0.091	0.034
TCI – SD1	*Pearsons's r*	0.157	0.251	-0.288	0.355
	p-value	0.592	0.349	0.218	0.178
	Spearman's rho	0.131	0.134	-0.129	0.400
	p-value	0.685	0.649	0.606	0.156
TCI – SD2	*Pearsons's r*	0.036	0.342	0.475*	0.429
	p-value	0.903	0.194	0.034	0.097
	Spearman's rho	-0.029	0.436	0.650**	0.272
	p-value	0.928	0.119	0.004	0.346
TCI – SD3	*Pearsons's r*	-0.044	0.179	-0.054	0.506*
	p-value	0.881	0.508	0.820	0.045
	Spearman's rho	-0.135	0.223	0.218	0.489
	p-value	0.675	0.444	0.385	0.076
TCI – SD4	*Pearsons's r*	0.830***	0.585*	0.133	0.032
	p-value	< 0.001	0.028	0.575	0.906
	Spearman's rho	0.714**	0.679*	-0.117	-0.143
	p-value	0.009	0.008	0.643	0.627
TCI – SD5	*Pearsons's r*	0.721**	-0.019	0.195	0.322
	p-value	0.004	0.943	0.411	0.224
	Spearman's rho	0.725**	0.324	-0.077	0.108
	p-value	0.008	0.258	0.763	0.713
TCI – SD TOT	*Pearsons's r*	0.618*	0.391	0.157	0.336
	p-value	0.019	0.134	0.509	0.203
	Spearman's rho	0.667*	0.595*	0.243	0.108
	p-value	0.018	0.025	0.332	0.713
TCI – SC1	*Pearsons's r*	0.151	0.162	0.442	-0.085
	p-value	0.606	0.580	0.051	0.753
	Spearman's rho	0.116	-0.145	0.547*	0.091
	p-value	0.720	0.620	0.019	0.757
TCI – SC2	*Pearsons's r*	-0.209	0.215	0.435	0.232
	p-value	0.474	0.424	0.071	0.424
	Spearman's rho	0.029	0.306	0.219	0.234
	p-value	0.929	0.287	0.382	0.421
TCI – SC3	*Pearsons's r*	-0.695**	-0.049	0.229	-0.215
	p-value	0.006	0.857	0.331	0.424
	Spearman's rho	-0.463	-0.116	0.177	-0.116
	p-value	0.130	0.924	0.481	0.694
TCI – SC4	*Pearsons's r*	0.263	0.776***	0.235	-0.237
	p-value	0.408	<0 .001	0.318	0.378
	Spearman's rho	0.147	0.826***	0.034	-0.257
	p-value	0.648	<0 .001	0.893	0.376
TCI – SC5	*Pearsons's r*	-0.463	-0.258	0.576*	0.469
	p-value	0.096	0.373	0.012	0.067
	Spearman's rho	-0.339	-0.075	0.468	0.374
	p-value	0.280	0.799	0.050	0.088
TCI – SC TOT	*Pearsons's r*	-0.197	0.204	0.456*	0.062
	p-value	0.499	0.450	0.044	0.820
	Spearman's rho	-0.145	0.270	0.351	0.234
	p-value	0.653	0.350	0.153	0.421
TCI – T1	*Pearsons's r*	0.165	0.581*	-0.324	-0.922***

	p-value	0.572	0.018	0.164	< 0.001
	Spearman's rho	0.174	0.414*	-0.324	-0.954***
	p-value	0.589	0.141	0.164	< 0.001
TCI – T2	*Pearsons's r*	-0.200	0.016	-0.376	-0.568*
	p-value	0.494	0.952	0.102	0.022
	Spearman's rho	-0.265	-0.168	-0.518*	-0.355
	p-value	0.406	0.565	0.028	0.213
TCI – T3	*Pearsons's r*	-0.200	0.151	**-0.530***	**-0.790***
	p-value	0.534	0.697	**0.016**	**< 0.001**
	Spearman's rho	-0.145	0.151	**-0.580***	**-0.666****
	p-value	0.653	0.697	**0.012**	**< 0.009**
TCI – T TOT	*Pearsons's r*	-0.013	0.320	**-0.460***	**-0.877***
	p-value	0.969	0.264	**0.041**	**< 0.001**
	Spearman's rho	-0.029	0.107	**-0.433**	**-0.749****
	p-value	0.930	0.715	**0.072**	**< 0.002**

* p < .05, ** p < .01, *** p < .001.

S6. Ophthalmological evaluation of patient group

Twenty patients affected by GO (all female; mean age: 43 ± 16 years) and ten healthy subjects (all female; mean age: 38 ± 18 years) were enrolled in this study. Both groups were homogeneous for gender and age and their demographical characteristic (Table S1).

Control group (HC) showed normal values of peripheral thyroid and absence of serological TRAb. Normal visual acuity, values of bulbar proptosis (15.2 ± 1.3 mm) and normal ocular evaluation were also observable in HC. Specific ocular findings of the GO patient group are reported in Table 1.

The subgroup analysis (by CAS, group I: CAS<3, n=8; group II: CAS≥3, n=12) was performed.

A correlation between CAS and proptosis value was found (Pearson's r = 0.755; p<0.001), and consequently, GO patients from group II show significant higher proptosis (proptosis =20.9 ± 1.8 mm) respect to Group I patients (proptosis = 17.9 ± 1.9 mm, p=0.005).

Table S6. Demographical and ocular findings of the study population.

Variable	GO (n=20)
Age, y (mean±SD)	43±16
Gender	20 female
Smokers N.(%)	10/20 (50%)
GD duration (months)	14.9±4.6
Peripheral thyroid function: • Euthyroid (without therapy) N. (%) • Euthyroid (ongoing therapy) N. (%) • Hyperthyroid (with therapy) N. (%)	2 (10%) 16 (80%) 2 (10%)
TRAb titer (mean±SD) U/liter	5.4±2.6
Duration of GO (months)	10.4±1.6
Ophthalmological evaluation	
Visual acuity (mean±SD)	1±0
Proptosis mm	19.1±2.4 (range 16-23 mm).
CAS (mean±SD)	2.1±1.52 (range 0-5)
CAS≥3 N. (%)	8 (40%)

Severity assessment	
Mild N. (%)	18 (90%)
Moderate to severe N. (%)	2 (10%)
Presence of diplopia N (%)	2/20 (10%)

Table S7. Summary of CANTAB neuropsychological tasks employed (modified by [57])

CANTAB tasks	Description	Performance indices
Visual memory Paired Associates Learning (PAL) [54]	Episodic memory and learning. It requires subjects to learn the location of 1, 2, 3, 6, and 8 visual pattern-location pairings. For participants who fail to complete all stages, an adjusted total is calculated that allows for errors predicted in the stages that were not attempted	PAL Total errors (adjusted), PAL Total errors (six shapes, adjusted), PAL means of Tentative and PAL First trial memory score
Spatial Working Memory (SWM) [55]	Working memory capacity and strategy use. It requires subjects to "search through" boxes on the screen to find individual "blue tokens" without returning to a box where one had previously been found	SWM Between errors (Total) (returning to a box where a token has previously been found), the SWM Between errors (four boxes), (six boxes), and (eight boxes), and the SWM Strategy
Rapid Visual Information Processing (RVP) [56]	Sustained attention. It requires subjects to detect infrequent three- digit sequences from among serially presented digits	RVPA' (sensitivity to the target) and RVP Mean latency

Table S8. Temperaments and Character Inventory (TCI) – Dimensions of Personality Traits

Temperaments	Subscales	Characters	Subscales
Novelty Seeking (NS)	Exploratory excitability (NS1) Impulsiveness (NS2) Extravagance (NS3)[3] Disorderliness (NS4)	Self-Directedness (SD)	Responsibility Vs. Blaming (SD1) Purposefulness Vs. Lack Of Goal Direction (SD2) Resourcefulness Vs. Inertia (SD3) Self-Acceptance Vs. Self-Striving (SD4) Congruent Second Nature Vs. Incongruent Habits (SD5)
Harm Avoidance (HA)	Anticipatory worry (HA1) Fear of uncertainty (HA2) Shyness/Shyness with strangers (HA3) Fatigability/Fatigability and asthenia (weakness) (HA4)	Cooperativeness (CO)	Social acceptance vs. intolerance (C1) Empathy vs. social disinterest (C2) Helpfulness vs. unhelpfulness (C3) Compassion vs. revengefulness (C4) Principles vs. self-advantage (C5)
Reward Dependence (RD)	Sentimentality (RD1) Openness to warm communication or social sensitivity (RD2) Attachment (RD3) Dependence on approval by others (RD4)	Self-Transcendence (ST)	Self-forgetful vs. self-conscious experience (ST1) Transpersonal identification vs. self-isolation (ST2) Spiritual acceptance vs. rational materialism (ST3)
Persistence (PS)			